



# Evaluating Cancer in the Particulate Matter Integrated Science Assessment and the Relationship with Diesel Exhaust Exposures

*Briefing for Thomas Burke, Deputy Assistant Administrator/EPA Science Advisor  
Office of Research and Development  
U.S. EPA*

Office of Research and Development  
National Center for Environmental Assessment

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# Goal of the Briefing

To provide context and background information for upcoming decisions on:

- (1) Scope and approach to evaluate cancer in the PM ISA
- (2) Agency position on conducting a Quantitative Risk Assessment on Diesel Exhaust

# Outline

## Part 1:

- Proposed Approach for Evaluating the Relationship Between Particulate Matter (PM) Exposure and Cancer in the Upcoming Integrated Science Assessment (ISA)
  - Conclusions for Long-term PM<sub>2.5</sub> Exposure and Cancer from 2009 PM ISA
  - IARC – Air pollution (and PM) and Cancer Evaluation
  - IARC vs. PM ISA
  - Proposed approach

## Part 2:

- Overview of Recent Diesel Engine Exhaust (DE) and Lung Cancer Issues
  - History
  - Recent studies
  - HEI Diesel Epidemiology Panel
    - Evaluation and Conclusions
    - Issues
  - Future Decisions

# **Part 1: Proposed Approach for Evaluating the Relationship Between Particulate Matter and Cancer in the Upcoming Integrated Science Assessment**



## Causality Determination for Long-term PM<sub>2.5</sub> Exposure and Cancer (2009 PM ISA): Suggestive of a Causal Relationship

### Epidemiology

#### Strengths:

- Multiple studies (original and reanalysis of Harvard 6 Cities and American Cancer Society cohorts, Adventist Health Study of Smog cohort, Netherlands cohort on diet and cancer, and a Norway cohort) have shown a consistent positive association between PM<sub>2.5</sub> and lung cancer mortality

#### Limitations:

- Few studies have examined the effect of PM on incident cancer cases
  - No studies have shown associations with PM<sub>2.5</sub> and lung cancer incidence

### Toxicology

#### Strengths:

- Ambient urban PM, emissions from wood/biomass burning, emissions from coal combustion, and gasoline and diesel exhaust are mutagenic
- PAHs are Genotoxic

#### Limitations:

- Animal toxicology studies did not focus on specific PM size fractions
- Little evidence of carcinogenicity in animal inhalation studies
- A few epigenetic studies have demonstrated that PM induces some changes in methylation

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- Lancet Oncology (December 2013)
  - *“The IARC Working Group unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as carcinogenic to humans (IARC Group 1), based on sufficient evidence of carcinogenicity in humans and experimental animals and strong mechanistic evidence.”*
- Monograph has not yet been released (~ end of 2015).
  - The following information is based on conversations with Dana Loomis at IARC, a presentation held at EPA on the IARC conclusions, and presentations from a symposium at SOT by members of the IARC Working Group



## IARC Monograph: Epidemiology Studies

- Evaluated a number of new studies that were published after completion of the 2009 PM ISA (6 – U.S., 4 – Europe, 3 – Asia)
- Conducted a meta-analysis of lung cancer incidence and mortality from studies published since 1999 (Hamra et al. 2014 – EHP)
  - Generally consistent, positive associations for PM<sub>2.5</sub> with the strongest evidence from U.S.-based studies
  - Less consistent evidence for PM<sub>10</sub>
- Evaluated the relationship between PM exposure and cancer taking into consideration:
  - Smoking status
  - Exposure assessment
  - Confounder adjustment

RR for PM<sub>2.5</sub>: NA 1.11, Europe 1.03, Japan/China 1.13, Overall 1.09

Fixed monitor versus modeling

Confounder adjustment: smoking status, socioeconomic status (SES)/income, education, and occupation (which includes occupational exposure)



## IARC Monograph: Toxicological Studies of Tumor Formation

Note: Selection of toxicological studies for evaluation was conducted without a systematic approach as is done within the ISA.

- **Outdoor air**

- Few studies have examined tumor formation in animals exposed to outdoor air pollution by inhalation
- Enhanced formation of urethane-induced lung tumors was observed in mice exposed to traffic-related air pollution in São Paulo, Brazil

- **PM extracts**

- Tumor formation was observed in rodents that were exposed by subcutaneous injections
- PM from different cities had different carcinogenic potency

- **Diesel engine exhaust and emissions from coal and wood combustion**

- Earlier IARC evaluations reported increased lung tumors in rodents
- It is unclear whether recent inhalation studies (LRR) were included. These used relevant concentrations (1 mg/m<sup>3</sup> and below) of diesel exhaust and wood smoke and found no evidence of tumor formation in lung (or micronuclei formation in WBCs)

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Concern about route of exposure: subcutaneous vs inhalation

Concern about extracts: may not mimic bioavailability in vivo

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## IARC Monograph: Other Toxicological Studies and Occupational Studies

- **Outdoor air**

- Germline mutations and epigenetic modifications were observed in mice exposed to traffic and steel mill-related air pollution
- Genotoxicity, including micronuclei formation and chromosome aberrations, and epigenetic modifications were observed in white blood cells from people exposed occupationally to polluted outdoor air in Europe, Asia, and Africa

- **PM extracts**

- Mutagenic activity of PM extracts has been demonstrated in bacterial systems

Concern about exposure characterization (in terms of PM) in occupational studies

Concern about the relevance of extract studies – may not mimic bioavailability in vivo

## Differences Between Approaches Taken by IARC and PM ISA

- Different scope between IARC and ISA
  - IARC included studies of air pollution as a whole, PM mass, PM sources, and individual PM components
    - Conclusion was for PM as a whole, not by size fraction
      - As a result, ISA could not just reference IARC monograph
  - ISA is tasked with answering the question: "Is there an independent effect of PM on cancer at relevant ambient concentrations?"
  - Scope of the PM ISA:

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- Different literature search strategies used by IARC and ISAs
  - IARC relied on scientific judgment, specifically for toxicological studies; whereas ISA uses a defined literature search process

## Differences Between Approaches Taken by IARC and PM ISA (Cont.)

- Weight placed on lines of evidence differs between IARC and ISA
  - Both IARC and ISA place a lot of weight on epidemiologic studies. In both, studies are evaluated across geographic locations.
  - The ISA prioritizes animal studies at relevant inhalation concentrations; whereas IARC evaluates animal studies conducted at various concentrations and through routes of exposure outside inhalation (e.g., intratracheal instillation, injection).
  - The ISA considers mechanistic in vitro studies as supportive evidence; whereas IARC places a lot of weight on these studies.
- Causal determination frameworks differ between IARC and ISA
  - IARC assess strength of evidence in human and animals separately and then makes a determination based on level of carcinogenicity; no concentration cut off
  - ISAs integrate evidence across disciplines to make a determination between an exposure duration and broad outcome category (e.g., cardiovascular, respiratory) at relevant ambient concentrations

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This will be detailed in the PM Integrative Review Plan that we are currently working on in collaboration with OAQPS. Expected release for review by the CASAC will occur by the end of the year.

## **Part 2: Overview of Diesel Engine Exhaust (DE) and Lung Cancer**

# Diesel Exhaust

- DE is a complex mixture of PM and gases
  - Therefore, the evaluation of DE relates to the PM ISA and the evaluation of gaseous exhaust components such as PAHs
- Using elemental carbon (EC) concentrations as a surrogate, Diesel PM is approximately 4-30% of total PM<sub>2.5</sub> mass
- DE is prominent in some areas including urban environments where there is a large proportion of buses and trucks with diesel engines
- DE is of concern to Environmental Justice communities
- DE contains a climate change element in black carbon (BC)

## History

- DE is a complex mixture of particulate matter and gases
- In the 1980's and 1990's EPA/NCEA developed Air Quality Criteria Documents (AQCDs) for the criteria air pollutants and Health Assessment Documents (HADs) for some other priority pollutants
  - Currently, IRIS serves the purpose that HADs provided in the past
- EPA completed a Diesel HAD in 2002
  - Reviewed by CASAC
  - DE HAD Conclusions:
    - "Long-term (i.e., chronic) [DE] inhalation exposure is likely to pose a lung cancer hazard to humans"
    - "Available data are inadequate to confidently derive a cancer unit risk estimate for DE or its component, diesel particulate matter", and subsequently the inability to conduct a quantitative risk assessment (QRA)
- Conclusions of the DE HAD has formed the Agency's stance on DE up to this point

## New Studies

- Since 2002:
  - Two studies were published that added to the epidemiologic evidence and brought forth the question as to whether the scientific data available is now sufficient to conduct a QRA
    - Diesel Exhaust in Miners Study (DEMS)
      - Attfield et al. (2012) – full cohort
      - Silverman et al. (2012) – nested case-control
        - Study of 8 non-metal mining facilities; 12,315 workers
    - Trucking Industry Study (TriPS)
      - Garshick et al. (2012)
        - Male workers employed in the unionized U.S. trucking industry in 1985; 31,135 workers
  - IARC concluded that “diesel exhaust is a cause of lung cancer” in 2013



## Response to New Studies

- Administrator Jackson was briefed after the DEMS and TriPS studies were published in order to decide whether EPA was going to revise the Diesel HAD and conduct a QRA
  - This briefing stemmed from numerous stakeholders (Environmental Justice and others) asking “Will EPA update the DE HAD?” and, subsequently conduct a QRA for DE?
  - The Administrator was presented with pros/cons of various options and decided that the Agency should ask HEI for an evaluation of the new DE epidemiology studies to assess whether they were suitable for conducting a QRA

## HEI Diesel Epidemiology Panel

- In response to the DEMS and TriPS studies, at the request of industry and the EPA, HEI convened a Diesel Epidemiology Panel
  - Tasked with evaluating the suitability of using data from the DEMS and TriPS studies in a QRA
- In March 2014, 1-day workshop was held where the investigators of both studies extensively detailed all aspects of each study with a focus on the exposure assessment conducted and statistical analyses performed
  - The HEI panel was able to ask some questions, as was the audience, which was comprised of industry and government representatives

## Evaluation/Conclusions

- HEI Diesel Epidemiology Panel
  - Evaluated two main issues:
    1. The influence of smoking, radon, and other factors
      - Conclusion: No evidence of confounding that would prevent a QRA, but some uncertainties would need to be addressed
    2. The historical estimates of exposure to DE
      - Both studies use a measure of elemental carbon (EC) (DEMS: respirable EC [REC]; TrIPS: sub-micron EC [SEC])
      - Conclusion: Exposure assessments had numerous strengths and underwent numerous sensitivity and validity analyses
        - Uncertainties: exposure levels in earlier time periods of studies, and how to consolidate the two different exposure metrics used in the DEMS and TrIPS studies

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Smoking, radon, and other factors

TrIPS:

No individual data on smoking status, but a previous analysis performed indirect adjustment for smoking status

Healthy worker bias contributed some uncertainty

DEMS:

Nested case-control allowed for detailed evaluation of confounders and ability to parse out smoking variable

Concluded that smoking control was reasonable

Potential confounding by residential radon examined, but data was sparse

Observed some reduction in lung cancer estimates when controlling for radon

DE Exposure

TrIPS:

Low exposures compared to workers in DEMS

Exposure estimates were validated using external data

Unclear how well SEC captures DE exposure

EC modeled using coefficient of haze (COH), unclear how well it captures regional differences and fuel changes

DEMS:

Validation datasets

Surface Exposures similar to those in TrIPS for exposure intensity. For cumulative exposure mean underground tenure in DEMS was 8 years, but 22 years for TrIPS.

CO used to estimate REC concentrations, but facility-specific information

# Issues

- Issues
  - Two industry funded papers were published during the HEI panel's evaluation
    - Moolgavkar et al. (2015) – Two-stage Clonal Expansion Model focusing on DEMS
      - Concluded entire risk of lung cancer attributed to one mine
    - Crump et al. (2015) – Evaluation of exposure assessment in DEMS
      - Calculated 6 different estimates of REC and reported similar results using each exposure estimate
      - Stepwise analysis dropping out each mine one at a time and reported similar results regardless of the mine excluded

## Issues (cont.)

- The HEI panel was not tasked with evaluating these studies. However, the panel did compare the results with the DEMS study and will put the results of these studies in the context of the DEMS study in the final report
  - Moolgavkar et al. (2015)
    - Panel noted it was a post hoc analysis and has some inherent flaws that the authors have not addressed
    - Additional work is needed to address the applicability of biologically based models and how they are interpreted in the context of results from epidemiologic studies
  - Crump et al. (2015)
    - Drop out analysis (i.e., removing each mine from the analysis one at a time) confirms the results of the DEMS study, which is one of the analysis the panel said was needed to evaluate the DEMS results
    - Results do not support conclusions of Moolgavkar et al., which attribute results of the DEMS to one mine

## Deliberative Process / Ex. 5

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### Deliberative Process / Ex. 5

The EJ community has a number of perceived potential benefits, such as greater impetus for state/local emissions reductions.

Engine turnover: This message is conveyed in the outreach efforts as depicted in the additional slides provided. The HEI ACES (Advanced Collaborative Emissions Study) has provided valuable information on the differences in emissions and toxicity of the legacy diesel engines compared to those complying with our on-highway regulations.

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- Is additional information needed to inform either decision?